Effect of Intensive Glycemic Control and Diabetes Complications on Lower Urinary Tract Symptoms in Men With Type 1 Diabetes

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study

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OBJECTIVE — Although diabetes is known to result in lower urinary tract symptoms (LUTS) in men, it remains unclear if glycemic control can mitigate urinary symptoms. We studied how diabetic characteristics are related to LUTS in the men who completed the urological assessment component (UroEDIC) of the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study of the Diabetes Control and Complications Trial (DCCT) participants.

RESEARCH DESIGN AND METHODS — Study participants were men who completed the UroEDIC questionnaire at the year 10 DCCT/EDIC follow-up examination, which included data on genitourinary tract function and the American Urological Association Symptom Index (AUASI). Analyses were conducted to assess how treatment arm and diabetes characteristics were associated with LUTS using logistic regression.

RESULTS — Of the 591 men who completed the AUASI questions, nearly 20% (n = 115) had AUASI scores in the moderate to severe category for LUTS (AUASI score ≥8). No associations were observed between LUTS and treatment arm, or A1C levels at the DCCT baseline or end-of-study or at the year 10 EDIC (UroEDIC) examination. Of the diabetes complications studied, only erectile dysfunction at the UroEDIC examination was associated with LUTS.

CONCLUSIONS — These data from the UroEDIC cohort do not support the assumption that intensive glycemic control results in decreased lower urinary tract symptom severity in men with type 1 diabetes. This result may be due to a true lack of effect, or it may be due to other factors, for example, the relatively young age of the cohort.

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Diabetes and urologic diseases are very common health problems that markedly increase in prevalence and incidence with advancing age (1). Diabetes, which has been associated with an earlier onset and increased severity of urologic diseases, often results in costly and debilitating urologic complications. These urologic complications include bladder dysfunction and have a profound effect on the quality of life for men with diabetes. Specifically, over 50% of men with diabetes experience some kind of bladder dysfunction (2). In its most severe form, this dysfunction termed "bladder cystopathy" has been classically described as diminished bladder sensation, poor contractility, and increased postvoid residual urine (3). However, current understanding of diabetic bladder dysfunction reflects a progressive condition encompassing a broad spectrum of bladder disorders including lower urinary tract symptoms (LUTS) of urgency, frequency, nocturia, and incontinence. LUTS are the most common manifestation of diabetic bladder dysfunction, whereas bladder cystopathy is relatively uncommon and most likely represents end-stage bladder failure with symptoms of infrequent voiding, difficulty initiating voiding, and postvoid fullness.

The Diabetes Control and Complications Trial (DCCT) and its long-term observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, have demonstrated that intensive diabetes therapy reduces the development and progression of many diabetes complications, including retinopathy, nephropathy and peripheral neuropathy (4). Furthermore, observational studies have found that markers of more severe diabetes, including poor levels of glycemic control, are associated with an increased risk of LUTS (5). However, in many of these studies, LUTS was defined as including diagnoses or mark-

ers of benign prostatic hyperplasia and were limited by the inclusion of a relatively small sample of diabetic men. In addition, most of the men with diabetes in these studies had or were presumed to have type 2 diabetes. To the best of our knowledge, no data from randomized trials exist to substantiate whether intensive glycemic control can in fact reduce the risk of subsequent adverse lower urinary tract symptoms in men with type 1 diabetes.

We examined if glycemic control and other clinical diabetes-related factors affect the risk of LUTS among the men who participated in the UroEDIC portion of the DCCT/EDIC study. The DCCT was a randomized controlled clinical trial designed to identify the impact of glycemic control on the development and/or progression of microvascular complications; the EDIC study is the long-term epidemiologic follow-up of the trial participants.

RESEARCH DESIGN AND METHODS

DCCT/EDIC participation

The inclusion and exclusion criteria for the DCCT and the treatment protocol have been described in detail previously (6). Briefly, 1,441 subjects between 13 and 39 years of age (53% male) with type 1 diabetes were recruited between 1983 and 1989 to participate in the DCCT in two cohorts. The primary prevention cohort consisted of 726 subjects with no retinopathy, a urinary albumin excretion rate (AER) <40 mg/24 h, and diabetes duration of 1–5 years at baseline. The secondary intervention cohort consisted of 715 subjects who had nonproliferative retinopathy, urinary AER ≤200 mg/24 h, and diabetes duration of 1–15 years. Individuals were excluded if they had hypertension (defined by systolic ≥140 or diastolic ≥90 mmHg), a history of symptomatic ischemic heart disease, or the presence of symptomatic peripheral neuropathy.

The 1,441 subjects were randomized to receive either intensive or conventional diabetes therapy. Intensive treatment consisted of insulin administered three or more times per day by injection or by continuous subcutaneous infusion with an external pump. Frequent daily self-monitoring of capillary glucose levels was performed, and the results, coupled with anticipated meal content and exercise, were used to adjust insulin doses. Treatment goals were preprandial blood glucose levels between 70 and120 mg/dl (3.89 and 6.66 mmol/l), postprandial blood glucose levels <180 mg/dl (9.99 mmol/l), a weekly 0300 h measurement >65 mg/dl (3.61 mmol/l), a monthly measured A1C level within the nondiabetic range (<6.05%), and avoidance of severe hypoglycemia. Conventional therapy consisted of one or two daily insulin injections; the treatment goal was freedom from symptoms of hyperglycemia and frequent or severe hyperglycemia. The intensive and conventional treatment groups maintained a separation of median A1C level of about two percentage points throughout the DCCT (7.1% compared with 9.0%; $P < 0.001$). The DCCT was terminated in 1993 when the principal study question concerning treatment effects had been answered; the mean duration of follow-up in the DCCT was 6.5 years. At the end of the DCCT, participants were referred to their own health care provider for ongoing care. In 1994, 1,394 (96%) of DCCT subjects, 687 from the intensive arm and 688 from the conventional arm, agreed to participate in the EDIC follow-up study, which included annual examinations for complication status (7).

UroEDIC participation

All men enrolled in EDIC at year 10 (n = 713) were invited to participate in the UroEDIC Study, an ancillary study to examine the presence of urological complications, including lower urinary tract symptoms and erectile dysfunction. Of these, 591 (83%) consented to participate in UroEDIC and completed the questions regarding LUTS, as noted below. The institutional review board of each participating center approved the study, and a certificate of confidentiality was issued for this study by the federal government.

Assessment of lower urinary tract symptoms

Lower urinary tract symptom severity was assessed at the year 10 annual examination with the American Urological Association Symptom Index (AUASI) (8). The AUASI is a standardized seven-item questionnaire that quantifies the presence and frequency of the following lower urinary tract symptoms: nocturia, frequency, urgency, weak urinary stream, intermittency, straining, and the sensation of incomplete emptying. Scores on the index range from 0 to 35, with widely accepted cut points of 0–7, 8–19, and 20–35 designated as none/mild, moderate, and severe LUTS, respectively (9). Because there were relatively few men with AUASI scores above 20 in the EDIC study, men with AUASI scores ≥8 were considered together in a category of moderate/severe LUTS.

The seven lower urinary tract symptoms assessed in the AUASI were additionally categorized as irritative (or storage) or voiding (or obstructive) symptoms. Irritative symptoms included frequency, urgency, and nocturia, while obstructive symptoms included weak urinary stream, intermittency, straining, and the sensation of incomplete emptying.

Diabetes measurements

A1C was measured at baseline and quarterly during DCCT and annually in EDIC as previously described. For purposes of this analysis, we used A1C levels measured at baseline, the end of the DCCT, and at year 10 in EDIC (concurrent with the UroEDIC assessment) (10).

Diabetes complications

Peripheral neuropathy status in the DCCT was defined by the presence of definite clinically evident distal symmetrical polyneuropathy and an abnormal nerve conduction study or based on responses to the Michigan Neuropathy Screening Instrument during EDIC (11). Neuropathy was defined to be present with more than six positive responses on the Michigan Neuropathy Screening Instrument questionnaire or a score >2 on the examination—thresholds defined by prior validation studies (11,12). Retinopathy was assessed annually in the EDIC in one-quarter of the cohort and in all participants at EDIC years 4 and 10 using stereoscopic fundus photographs that were centrally graded using the Early Treatment Diabetic Retinopathy Study (ETDRS) (13) scale of 0–23 (1–11 = nonproliferative, ≥12 = proliferative). Albumin excretion rate (AER) was measured in half the cohort annually. Nephropathy was defined as microalbuminuria if AER was 40–299 mg/24 h or albuminuria if AER was ≥300 mg/24 h. The extent of atherosclerosis was assessed by measurement of intima-media thickness of the internal and common carotid arteries from centrally graded carotid ultrasonography (14) at EDIC year 1 and 6 and by measurement of the percentage of coronary artery calcification present on centrally graded computed cardiac tomography conducted during EDIC years 6–7 (15). Erectile dysfunction was defined in a binary fashion based on responses to the

Table 1—*Clinical characteristics of the male UroEDIC cohort*

	DCCT baseline (1983–1989)			Year 10 EDIC (2003)		
	Conventional	Intensive	*P*	Conventional	Intensive	*P*
n	302	289		302	289	
Sociodemographic characteristics						
Age (years)	27.6 ± 6.7	27.4 ± 6.8	0.90	44.6 ± 6.6	44.7 ± 6.6	0.89
Race*						
White, not of Hispanic origin	293 (97.0)	277 (95.8)		293 (97.0)	277 (95.8)	
Black, not of Hispanic origin	4 (1.3)	7 (2.4)	0.48	4 (1.3)	7 (2.4)	0.48
Hispanic	4 (1.3)	2 (0.7)		4 (1.3)	2 (0.7)	
Asian or Pacific Islander	1 (0.3)	3 (1.0)		1 (0.3)	3 (1.0)	
Married	169 (56.0)	146 (50.5)	0.19	223 (75.9)	221 (78.4)	0.47
Cigarette smoker†	53 (17.5)	58 (20.1)	0.43	98 (33.0)	99 (34.7)	0.66
Diabetes treatment and control						
Cohort						
Primary number	159 (52.6)	138 (47.8)	0.23	—	—	0.23
Secondary number	143 (47.4)	151 (52.2)		—	—	
Diabetes duration (years)	5.1 ± 3.9	5.7 ± 4.1	0.06	21.7 ± 4.6	22.6 ± 4.9	0.04
A1C	8.9 ± 1.5	8.9 ± 1.5	0.59	7.7 ± 1.3	7.8 ± 1.2	0.13
Insulin dose (units · kg^{-1} · day^{-1})	0.63 ± 0.24	0.67 ± 0.25	0.08	0.68 ± 0.23	0.73 ± 0.27	0.03
Microvascular complications						
Retinopathy‡						
Nonproliferative or none	302 (100.0)	289 (100.0)	0.62	143 (47.4)	208 (72.0)	<0.001
Proliferative	0 (0.0)	0 (0.0)		159 (52.6)	81 (28.0)	
Nephropathy						
None (AER§ <40)	289 (95.7)	274 (94.8)		205 (67.9)	219 (75.8)	
Microalbuminuria (40 ≤ AER < 300)	13 (4.3)	15 (5.2)	0.61	48 (15.9)	58 (20.1)	<0.001
Albuminuria (AER ≥300)	0 (0.0)	0 (0.0)		49 (16.2)	12 (4.2)	
Hypertension¶	0 (0.0)	0 (0.0)	—	155 (52.2)	113 (39.6)	0.002
Creatinine clearance (ml/min per 1.73 m^2)	132.2 (26.0)	133.1 (31.3)	0.87	117.5 (28.9)	122.5 (28.9)	0.03
Peripheral neuropathy#	20 (6.6)	23 (8.0)	0.53	227 (75.2)	189 (65.4)	0.009

Data are means ± SD or *n* (%). *Race was classified by the participant during the enrollment interview in the DCCT. †Defined as having ever smoked. ‡Determined by the Early Treatment Diabetic Retinopathy Study on a scale of 0–23; <12 nonproliferative, ≥12 proliferative. §Albumin excretion rate (mg/24 h). ¶Hypertension is defined as sitting systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or the use of antihypertensive medication. #Defined in the DCCT by the presence of definite clinically evident distal symmetrical polyneuropathy and an abnormal nerve conduction study, or in EDIC by more than six positive responses on the Michigan Neuropathy Screening Instrument questionnaire or a score >2 on the examination.

question: "Over the past 4 weeks, how would you rate your confidence that you get and keep your erection?" If the participant answered "very low" (1) or "low" (2), he was considered to have erectile dysfunction, while men who answered "moderate" (3), "high" (4), or "very high" (5) were considered to have no erectile dysfunction.

Statistical analysis

To test for differences between groups, the Wilcoxon's rank-sum test was used for quantitative variables, and the contingency χ^2 test was used for qualitative variables. The Fisher's exact test was used where appropriate. All analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC).

Logistic regression analysis was used to estimate the odds of moderate/severe LUTS associated with glycemic control and other diabetes complications. Statistical tests of the regression estimates were based on the χ^2 approximation for the likelihood ratio statistic, and 95% CIs were based on the Wald's test.

Univariate logistic regression models were fit without adjustment. Multivariate models were fit adjusting for the following a priori variables from Table 2: age, BMI, race, use of an α-blocking agent, smoking status, drinking status, level of education, martial status, and exercise status. Models also assessed interactions among these factors within diabetes treatment group.

RESULTS — Of the 713 men who participated in the year 10 EDIC examination, 591 (82.8%) completed the AUASI component of the UroEDIC questionnaire. No significant differences were noted at baseline between men who completed the symptom index compared with those who did not, with the exception that the UroEDIC participants had lower total cholesterol levels at DCCT baseline (179.1 vs. 171.5 mg/dl, $P = 0.022$) and lower mean blood pressure at EDIC year 10 (94.4 vs. 92.3 mmHg, $P = 0.025$) relative to nonparticipants.

The men who participated in the ancillary UroEDIC study were on average 44.6 ± 6.6 years of age (means ± SD) and had a mean A1C level at EDIC year 10 of 7.72 ± 1.3%. Table 1 presents socioeconomic and diabetic characteristics at DCCT baseline and at the year 10 UroEDIC examination by DCCT treatment assignment. At DCCT baseline, there were no significant differences between the treatment groups, demonstrating that the randomization process worked. However, of the men participating at the year 10 examination in EDIC, those randomized to intensive treatment were significantly more likely to have longer diabetes duration, use higher

Table 2—*Clinical characteristics of UroEDIC men according to presence or absence of moderate/severe LUTS at EDIC year 10*

	Moderate/severe LUTS	No/mild LUTS	*P*
n	115	476	
Sociodemographic characteristics			
Age (years)	46.6 ± 6.4	44.1 ± 6.6	<0.001
Race			
White, not of Hispanic origin	111 (96.5)	459 (96.4)	
Black, not of Hispanic origin	2 (1.7)	9 (1.9)	0.68
Hispanic	2 (1.7)	4 (0.8)	
Asian or Pacific Islander	0 (0.0)	4 (0.8)	
Married	83 (74.1)	361 (77.8)	0.40
Graduate education	26 (23.0)	107 (23.0)	0.99
Cigarette smoker	40 (35.4)	157 (33.5)	0.70
Drinking status	63 (55.8)	234 (50.2)	0.29
BMI (kg/m^2)	27.5 (3.9)	28.1 (4.2)	0.29
Sildenafil citrate use*	8 (7.0)	22 (4.6)	0.31
α-Blocker use	3 (2.8)	1 (0.2)	0.03
Diabetes treatment and control			
Diabetes duration (years)	22.0 ± 4.9	22.2 ± 4.7	0.53
Arm of DCCT			
Intensive	60 (52)	229 (48)	0.51
Conventional	55 (48)	247 (52)	
Cohort			
Primary	61 (53.0)	236 (49.6)	0.51
Secondary	54 (47.0)	240 (50.4)	
A1C at DCCT baseline (%)	8.8 ± 1.4	8.7 ± 1.5	0.38
DCCT mean A1C	8.1 ± 1.3	8.1 ± 1.4	0.80
Time weighted DCCT/EDIC mean A1C	8.1 ± 1.0	8.1 ± 1.1	0.84
Insulin dose ($units \cdot kg^{-1} \cdot day^{-1}$)	0.7 ± 0.2	0.7 ± 0.3	0.56
Microvascular complications			
Retinopathy†			
Nonproliferative or none	64 (55.7)	287 (60.3)	0.36
Proliferative	51 (44.3)	189 (39.7)	
Nephropathy			
None (AER‡ <40)	77 (67.0)	347 (72.9)	
Microalbuminuria (40 ≤ AER < 300)	22 (19.1)	84 (17.6)	0.31
Albuminuria (AER ≥300)	16 (13.9)	45 (9.5)	
Creatinine clearance (ml/min per 1.73 m^2)	117.5 ± 32.0	120.6 ± 28.2	0.26
Hypertension§	51 (45.1)	217 (46.3)	0.83
Peripheral neuropathy ever during DCCT and EDIC¶	92 (80.0)	324 (68.1)	0.01
Macrovascular complications			
Coronary calcification at EDIC year 10 >0	50 (48.1)	170 (38.6)	0.08
Carotid intimal medial thickness at EDIC year 1#	0.7 ± 1.7	0.2 ± 1.7	0.002
Carotid intimal medial thickness at EDIC year 6#	0.6 ± 1.7	0.3 ± 1.8	0.05
Total cholesterol (mg/dl)	181.6 ± 34.8	179.1 ± 33.3	0.61
Triglyceride (mg/dl)	102.3 ± 68.8	96.2 ± 65.0	0.53
Other complications			
Erectile dysfunction**	44 (39.3)	88 (19.2)	<0.001
Occlusion (ABI†† <0.9)	9 ± 7.8	38 ± 8.0	0.96
Clinically significant occlusion (ABI <0.8)	3 ± 2.6	15 ± 3.2	0.99
Calcification (ABI >1.3)	4 ± 3.5	22 ± 4.6	0.59

Data are means ± SD or *n* (%). All variables are at EDIC year 10 except where indicated. *Sildenafil citrate use reported during yearly EDIC drug inventory. †Determined by ETDRS <12 nonproliferative, ≥12 proliferative. ‡Albumin excretion rate (mg/24 h). §Hypertension is defined as sitting systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or the use of antihypertensive medication. ¶Defined in the DCCT by the presence of definite clinically evident distal symmetrical polyneuropathy and an abnormal nerve conduction study or in EDIC by more than six positive responses on the Michigan Neuropathy Screening Instrument questionnaire or a score >2 on the examination. #Combined intimal medial thickness. **Erectile dysfunction was assessed in UroEDIC with an anonymous questionnaire that included the erectile function, orgasmic, and desire domains of the International Index of Erectile Function (IIEF). A binary outcome variable for erectile dysfunction was created based on responses to the question: "Over the past 4 weeks, how would you rate your confidence that you get and keep your erection?" If the participant answered "very low" (1) or "low" (2), they were considered to have erectile dysfunction. If they answered "moderate" (3), "high" (4), or "very high" (5), they were considered to have no erectile dysfunction. ††The mean of the two brachial pressures was divided into each of the four systolic ankle pressures to yield four values for the ankle-brachial pressure index (ABI). The ABI selected for the analysis was the smallest of the four ratios.

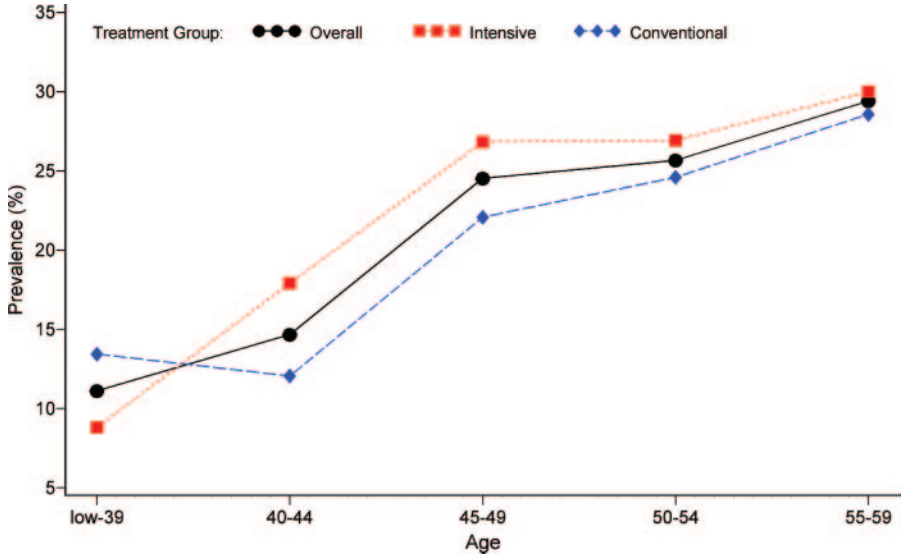

Figure 1—*Prevalence of LUTS by age and treatment group. LUTS is defined as an AUASI ≥8.*

doses of insulin, and have a higher creatinine clearance, but were less likely to have retinopathy, nephropathy, peripheral neuropathy, and erectile dysfunction relative to men randomized to the conventional arm.

Table 2 shows the univariate comparison between socioeconomic and diabetes characteristics and the presence of LUTS. Approximately 20% of the men reported moderate or severe LUTS. Of the 115 men with LUTS, only 6 men reported severe LUTS, with the remainder in the moderate range. Frequency of LUTS increased with age (Fig. 1). Compared with men without LUTS, men with LUTS were on average older, had peripheral neuropathy either during the DCCT or during EDIC, had a carotid intimal medial thickness that was higher at EDIC year 1, and reported erectile dysfunction. No differences were observed for the other socioeconomic or diabetes characteristics by LUTS status. However, the use of α-blockers was greater among men with LUTS compared with men without LUTS (2.8 vs. 0.2%, respectively, $P = 0.03$).

Adjusted for DCCT baseline factors, intensive therapy compared with conventional therapy did not reduce the risk of having moderate or severe LUTS (odds ratio [OR] 0.84, 95% CI 0.55–1.28, $P = 0.30$).

In multivariate analyses adjusted for other socioeconomic and diabetes characteristics at EDIC year 10, only erectile dysfunction was associated with LUTS (OR 2.54, 95% CI 1.53–4.20, $P = 0.0002$). No other diabetic characteristic, including DCCT treatment group assignment, cohort, or A1C level was associated with LUTS.

CONCLUSIONS— Among men with a duration of type 1 diabetes of ~20 years initially enrolled in a clinical trial designed to evaluate the impact of intensive versus conventional therapy on glycemic control, one in five reported moderate to severe LUTS. The prevalence of LUTS noted in the EDIC study is lower than estimates from epidemiologic studies (16,17), most of which were of community-dwelling men with few cases of diabetes. Estimates of the prevalence of LUTS among men of comparable age with diabetes in the Flint Men's Health Study or Olmsted County Study were ~38–58%; most of these men had type 2 diabetes (A.V.S., personal communication).

We had anticipated a higher prevalence of LUTS in the DCCT/EDIC cohort of men with type 1 diabetes. There may be several explanations for the lower observed prevalence in this study. First, control of glycemia in this population is undoubtedly better than that in the general population of men with type 1 diabetes, possibly contributing to a reduction in the severity of urinary symptoms. Second, the mean age of the men in the DCCT/EDIC is younger than when most men are bothered enough by urinary symptoms to visit a health care provider. Longer-term follow-up of the EDIC cohort may be required to determine if the prevalence and/or severity increases substantially as these men reach their 50s and 60s. Finally, another factor may be a selection bias of the participants who enrolled in the clinical trial; individuals were excluded from originally enrolling in the DCCT if they had any sign of advanced microvascular complications or other significant medical or psychiatric disorders. Whether men found eligible and who participated in the DCCT/EDIC through the year 10 UroEDIC study were less likely to develop moderate to severe LUTS over the course of follow-up compared with all type 1 diabetic men cannot be determined.

When a large number of clinical and demographic characteristics were considered, only erectile dysfunction was independently associated with LUTS. Several prior studies, which have mostly included men without diabetes, have found that self-reported erectile dysfunction and LUTS occur together (18). Given the exquisite sensitivity of erectile function to systemic diabetes perturbations, the association observed here is likely to be a better marker of the degree to which diabetes has disrupted vascular, endocrine, hormonal, and neuropathic function directly relevant to voiding function than the other diabetes complications that were included in this study. Examining how dysfunction in these body systems affects LUTS in future EDIC examinations will be important to better understanding this association.

We did not find a beneficial effect of intensive glycemic control on prevalence of moderate to severe LUTS. A1C levels at the beginning and end of the DCCT or at the year 10 EDIC examination, when urinary symptoms were assessed, were not associated with LUTS, as measured by the AUASI. Because diabetic cystopathy might be better reflected in irritative symptoms of the AUASI, we also conducted analyses stratified by irritative or obstructive grouping. However, we saw no difference from our primary results in these analyses.

Whereas there is general agreement that diabetes results in LUTS (1,19), the epidemiology of diabetes and LUTS is not clear. Much of the epidemiology in this area has been limited because prior studies that use markers of LUTS (e.g., transurethral resection of the prostate or TURP) (20) have included few men with diabetes, and/or included solely or primarily men with type 2 diabetes. Nonetheless, the Massachusetts Male Aging Study (21), Flint Men's Health Study (9), and others have consistently reported di-

abetes or glucose levels to be associated with an increased risk of LUTS with or without benign prostatic hyperplasia. Progression of LUTS has been reported to be greater in men with diabetes than in those without diabetes, in the absence of a difference in prostate volume growth between the two groups (22), suggesting a progressive impact on the bladder. However, these studies have not examined how glycemic control affects LUTS.

Whereas a significant number of studies have shown that diabetes affects the bladder (1), there may be several reasons why this study did not identify an association between glycemic control and LUTS. First, there may truly be no effect of glycemic control on LUTS in this cohort of men with type 1 diabetes. Because they have had type 1 diabetes for a significant period of time, the opportunity for glycemic control to influence LUTS may have passed. It may be due to the lack of metabolic memory, where effects of metabolic changes in the past (e.g., glycemic control) continue to exert an effect at a later time, regardless of current circumstances (23). For example, numerous other complications from diabetes have been positively affected by the use of intensive therapy and the improvement in glycemic control during the DCCT (4,15). It may be that there is no metabolic memory effect of effective glycemic control on the presence or development of LUTS. Second, it may also be that there are conflicting impacts of diabetes and glycemic control on the prostate and bladder, such that no effect is observed. If diabetes slows down prostate growth via its impact on testosterone and growth factors, it might reduce the risk of LUTS (via obstructive mechanism) and mask beneficial effects of glycemic control on bladder dysfunction. Third, as noted above, these men were relatively younger on average than the population of males that typically experience an increase in the frequency of LUTS. Thus, an insufficient number of men may have been in the primary risk period for developing LUTS, and additional follow-up of these men may reveal a different result regarding the relationship between glycemic control and LUTS.

In summary, data from this study do not support an association between glycemic control and a decrease in lower urinary tract symptoms. This may be due to the long period of time these men have had diabetes where the (beneficial) influence of glycemic control on bladder dysfunction was past. However, it may also be that these men were younger on average than when most men typically manifest LUTS. To assess the impact of glycemic control on LUTS, it will be important to reexamine this cohort when they are of an age when LUTS is more prevalent.

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